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| EXAMINER | |
|---|---|
| TUCKER, ZACHARY C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |

DATE MAILED: 04/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/776,002 | MITCHELL ET AL. | |
| | Examiner | Art Unit | |
| | Zachary C. Tucker | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-42 and 46-58* is/are pending in the application.

4a) Of the above claim(s) *32-42 and 46-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10Feb06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

As requested in the 10 February 2006 reply to the Requirement for Restriction, claim 42 has been amended and claims 43-45 have been cancelled.

### *Election/Restrictions*

On 4th January 2006, a Requirement for Restriction in the instant application was mailed to applicants. In the reply thereto, filed on 10 February 2006, applicants' counsel indicated election with traverse of Group I of the Requirement (claims 1-31, 57 and 58, drawn to imidazo[1,2-a]pyrazine compounds). This election is acknowledged. Applicants' traversal is based on allegation that for the examiner to search all of the claims would not constitute an undue burden. This is not found persuasive because according to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Applicant has made no rebuttal of the examiner's showing of separate classification and separate status in the art. Thus, a serious burden has been established.

Additionally, applicants' counsel states in the traversal argument that the search of the Group I compounds would of necessity also cover the art relevant to Group II-VI as a source for novelty- or obviousness-defeating prior compositions of matter. The examiner disagrees with this statement as well, because the patentability of Groups II-VI is not limited only to a consideration of whether the claimed compositions of matter

and methods are obvious or novel in view of the prior art. The patentability determination for the nonelected subject matter will involve a substantial amount of searching required to determine compliance with the first paragraph of 35 U.S.C. 112. This additional search is carried out to determine the state of the art at the time the invention was made and is generally not required in an examination of chemical compounds *per se*, although the examiner always bears in mind the requirements of 35 U.S.C. 112 in examination of any claimed subject matter. The state of the art with respect to the ability possessed by one of ordinary skill in the art to synthesize chemical compounds, such as those according to Group I of the Requirement, is revealed by the selfsame search required to determine novelty and non-obviousness of those claimed compounds. This is *not* the case with examination of methods and pharmaceutical compositions, such as those according to Groups II-VI, with respect to the requirements of the first paragraph of 35 U.S.C. 112. So, the searches required for the nonelected subject matter and for the elected subject matter are not of the same scope.

For the reasons provided above, the Requirement is still deemed proper and is therefore made FINAL.

Claims 32-42 and 46-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, but are subject to rejoinder upon the finding that the claims of the elected Group are in allowable form, as explained on pages 4 and 5 of the Requirement for Restriction letter.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula (1) compounds and the pharmaceutically acceptable salts thereof, does not reasonably provide enablement for the full scope of all prodrugs of Formula (1) compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
*In re Wands,* 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claims 1 and 28-31 are limited to compounds of Formula (1) having the structure depicted and the pharmaceutically acceptable salts of those compounds, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds of Formula (1) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only acylated derivatives, which are commonly cited as examples, and suggested as the preferred type of prodrug on page 16 of the instant

specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily even depend on the identity of the pharmacologically active agent formed from the prodrug for its patentability. A prodrug is not necessarily structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of compounds having Formula (1) are the nature of the invention.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

> Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the

metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically derived when the compounds in question are allegedly novel, as is the case with the compounds of Formula (1).

(F) The following passage is the direction provided for the synthesis of prodrugs of chemical entities of Formula (1). –

> The term "prodrugs" includes any compounds that become compounds of Formula I when administered to a mammalian subject, e.g., upon metabolic processing of the prodrug. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I.

No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than acylated derivatives.

(G) No working examples, out of the eleven preparative examples of compounds of Formula (1), of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of chemical entities having the Formula (1), a complete structure activity analysis of all of the entities falling within Formula (1) would have to be completed. This analysis would involve thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active chemical entities of Formula (1) *in vivo* identified. This research would potentially be inconclusive and could take years. A practitioner of ordinary skill in the art would necessarily also have to undertake an effort to make totally new compounds not bearing any structural similarity to the chemical entities having the Formula (1), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman, and polymeric forms of the compounds as well. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making

prodrugs of chemical entities having the Formula (1), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31, 57 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the phrase "or prodrugs thereof," referring to compounds of Formula (1), is recited. This language renders the scope of claim 1, and therefore all claims which depend from claim 1, indefinite in scope. Claims 2-31, 57 and 58 are included in this rejection because those claim depend from an indefinite base claim, and therefore, incorporate all of the limitations of that indefinite base claim.

Applicants may opine that one of ordinary skill understands exactly what the term "prodrug" signifies. The examiner is not pretending that one of ordinary skill does not understand what *function* a prodrug serves, but that is not the issue here. What is claimed is chemical compounds which serve as a prodrug for the compounds of Formula (1). The claim, therefore, is drawn to a group of *molecular structures*, that when subjected to a biological milieu in a live animal, will be metabolically converted to a compound of Formula (1). One of ordinary skill cannot possibly be aware of the full scope of all different molecular arrangements which will provide the compounds (1) upon being metabolized, in any and all mammalian species. Page 16 of the specification only provides a few examples of what applicants intend the term to encompass. The only type of prodrug discussed in the instant specification is acylated (ester) derivatives.

As evidenced by the Al-Dabbagh and Smith reference, cited *supra*, in the rejection of the claimed prodrugs under the first paragraph of 35 U.S.C. 112, animals will differ significantly in the manner that xenobiotics are metabolized. Therefore, a compound that is a prodrug in humans is not necessarily a prodrug in a cat, for example. This fact further confounds any effort to determine which group of molecular structures would provide the prodrugs specified in instant claim 1.

It is recommended that applicants delete "or prodrugs thereof" from the instant claims.

Claims 28-31 are found to be further indefinite, in addition to being indefinite for depending from an indefinite base claim (1), because the phrase "or form thereof" is not understood. Exactly what form is being referred to is not made clear by the claim language, as no antecedent basis is provided in instant claim 1 for any "form" of the compounds of that claim being referred to in dependent claims 28-31. As such, the full scope of claims 28-31 cannot be determined. Deletion of the phrase "or form thereof" in all occurrences would overcome this additional ground of rejection under 35 U.S.C. 112, second paragraph.

***Specification***

Applicants' request that the objection to the title of the application be held in abeyance, pending allowance, is honored.

***Information Disclosure Statement***

Signed and initialed forms PTO-1449 which accompanied the 10th February 2006 submission of an Information Disclosure Statement in the instant application are enclosed with this Office action. Each cited document listed on the second page of the

PTO-1449 form has been lined through by the examiner, as these citations are not compliant with 37 C.F.R. 1.98 (a)(3)(i) and 1.98(b)(5), as no publication dates for the documents were provided. The examiner has, however, conducted a cursory review of those lined-through documents.

***Allowable Subject Matter***

Claims 1-31, 57 and 58 would be allowable if rewritten or amended to overcome the rejections under 35 U.S.C. 112, set forth in this Office action.

A search of the prior art did not afford any disclosure of, nor any teaching or suggestion rendering Formula (1) compounds obvious. As indicative of the state of the closest prior art, the examiner would cite US 6,919,341 (Paruch et al), which qualifies as prior art as of the effective filing date of 19 April 2002, before the effective filing date of the instant application. The compounds of the Paruch et al patent are kinase inhibitors, based on the same imidazo[1,2-a]pyrazine nucleus as the instantly claimed compounds, but with a different substitution pattern around that nucleus. The Paruch et al compounds lack the required heteroaryl or phenyl ring at the position corresponding to "W" in Formula (1) of the instant claims, and also lack the "X" –containing aryl ring on the core of the Formula (1) compounds according to the instant invention.

Applicants have filed several patent applications, claiming similar compounds to those of the instant application, but none of these other applications overlaps with the subject matter of the instant application, specifically, the "W" substituent, wherein "W" is aryl or heteroaryl, is not part of the compounds according to applicants' copending applications.

Upon amendment of the instant claims to overcome the rejections set forth herein, the claims of Groups II, IV and V will be *sua sponte* rejoined. At such time, a rejection of claims 38-41 will be set forth, under the first paragraph of 35 U.S.C. 112. The broadest reasonable interpretation of claims 34 and 46 reads on treatment of diseases wherein inhibition of kinase activity up-modulates the effects of the disease, that is, makes the disease *worse*, because the term "modulate" is limited neither to up-modulation nor down-modulation. Claims 34 and 46 are also indefinite in scope, because of the fact that kinases are ubiquitous in animals and the effects of inhibiting all kinases are not known. Thus, it would not be possible for one of ordinary skill to identify the group of diseases or disorders contemplated by the language of instant claims 34, 46, or any claim depending from those claims.

Claims 38-42, though they specify "in an amount sufficient to detectably inhibit ___ activity *in vitro*," are not limited to *in vitro* methods. Those claims do not limit the inhibition of the specified kinases to inhibitions occurring *in vitro*, only that the amount be the same as would have been required for said inhibition *in vitro*. Additionally, the term "amount" is not proper; the term "concentration" would be more appropriate in the context of the methods according to claims 38-42.

Claims 52-55 are limited to *in vitro* methods, as the phrase "in a sample" cannot fairly be interpreted as reading on "inside animal or a patient."

Applicant should not interpret any of the preceding comments as an indication that the withdrawn claims have been examined, only that they have been *read*, to determine what they cover. The MPEP directs the examiner to do so when making Requirements for Restriction, in chapter 814.

***Conclusion***

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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